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Applications of Heteroisobenzofurans in Natural and Non-natural Product Synthesis

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ABSTRACT

The heteroanalogue of isobenzofurans, commonly known as heteroisobenzofurans, is a prevalent intermediate for the synthesis of various important heterocyclic compounds, and interest in heteroisobenzofuran chemistry has greatly increased recently. Heteroaromatic isobenzofurans are still in their infancy compared to isobenzofurans, and many potential molecules have yet to be produced. This problem can be solved by creating innovative heteroaromatic assemblies with biological importance and forming new heteroisobenzofurans. Natural products, both those obtained from nature and those produced synthetically, have gained enormous importance both as medications and as building blocks for intricate compounds. The application of various heteroisobenzofurans in the synthesis of biologically important natural and non-natural products will be discussed in this chapter, along with a brief overview of the synthesis and reactivity of this privileged reactive intermediate.

Keywords: Heteroisobenzofurans; Heterocycles; Natural Products; Organic Synthesis; Cycloaddition; Diels-Alder Reaction; Reactive intermediates

Introduction

Isobenzofurans are a kind of heterocyclic molecule that have a benzene ring fused to the 3,4-positions of a furan ring. They are also referred to as Benzo[c]furans and 2-Oxa-2H-isoindenes since they are isomers of benzofurans. They quickly polymerize and are very reactive. It is known that stable compounds with quite intricate structures and isobenzofuran moieties exist despite their instability. Similar to isoindole, the isobenzofuran nucleus has ten π-electrons. This chemical has a higher reactivity than isoindole. The isobenzofuran ring is highly reactive at the 1- and 3-positions and readily engages in a number of chemical reactions that allow the benzene ring to regenerate its aromaticity.

Nevertheless, the high reactivity of isobenzofurans comes at the expense of their poor stability. Since it is readily accessible and generally stable, 1,3-diphenylisobenzofuran is the most widely used isobenzofuran derivative. Isobenzofuran is approximately ten times more reactive but is very difficult to prepare and purify. As a result, it should be produced in situ and used in conjunction. Although the chemistry of isobenzofuran is well established, the chemistry of heteroisobenzofuran is still evolving, and several possible results are yet to be discovered.

Since the heteroisobenzofuran moiety already has a heterocyclic ring, it always produces new heterocyclic compounds after the reaction. It is well known that many heterocyclic frameworks can be classified as privilege compounds. In the rapidly developing area of heterocyclic chemistry, researchers continually discover new and intriguing applications for heterocyclic compounds. Heterocycles are essential in organic chemistry since they make over fifty percent of all known organic compounds. Heterocyclic moieties are often found in natural products, alternative fuels, herbicides and pesticides, drugs, and macromolecules (Panda, 2020). These molecules have been synthesized using a variety of methods (Panda, 2023), including click reactions, novel multicomponent domino processes (Panda *et al.,* 2010), and traditional condensation techniques. Moreover, green and sustainable chemists have a keen interest in developing novel methods for synthesising heterocycles (Panda *et al.,* 2011). By using heterocycles, it is possible to alter the solubility, lipophilicity, polarity, and hydrogen bonding capabilities of biologically active substances, which improves the ADME/Tox characteristics of medications or drug candidates. Drugs now include more heterocycles than ever before thanks to improvements in synthetic techniques like metal-catalyzed cross-coupling (Panda & Albano, 2021) and hetero-coupling processes (Panda & Sarkar, 2013), which provide easy access to a range of functionalized heterocycles. Contrarily, a large number of heterocyclic lead molecules were obtained from natural sources, and then their structures were amended by medicinal chemists. Hence, heterocycles are crucial for medicinal chemists, as they may be used to increase the accessible drug-like chemical space and support more successful drug development processes.

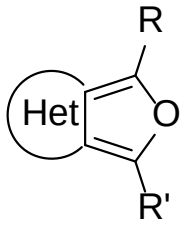

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Figure 1: Heteroisobenzofuran

Literature Review

The synthesis of heteroisobenzofuran was well documented in a nice review by Basak and co-workers (Basak *et al.,* 2001). Heteroisobenzofuran can be synthesized through: (a) the thermolysis of 1,4-epoxide; (b) acid-catalyzed cyclization; (c) organometallic reagent-promoted cyclization; (d) the Rh-catalyzed Hamaguchi-Ibata reaction; (e) the Pummerer reaction of heteroaromatic ortho-keto sulfoxides; (f) the reaction of o-alkynyl carbonyl compounds with chromium carbene reagents; (g) base mediated elimination pathway. Various synthetic strategies for the preparation of heteroisobenzofuran are shown in figure 2.

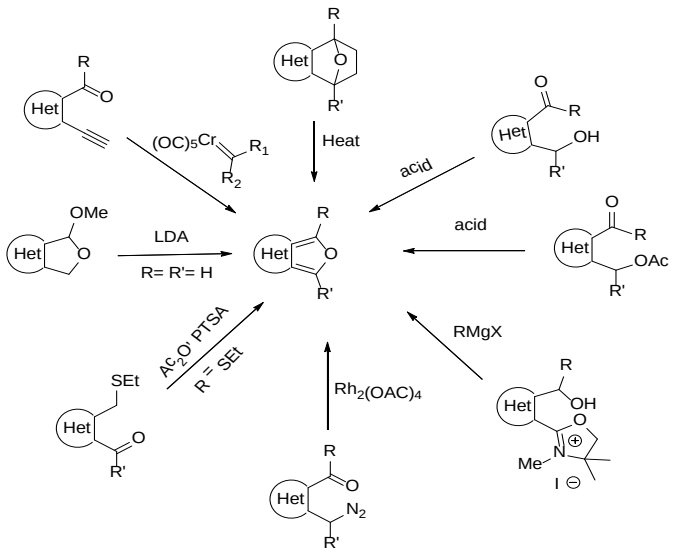

Figure 2: Synthesis of Heteroisobenzofuran

Heteroisobenzofuran is well documented in the literature due to its novel reactivity profile. The 10 π-electron system behaves as a suitable diene in a [4+2]-type cycloaddition reaction. Since in the Diels-Alder reaction, the nature of diene and dienophile plays a crucial role in the output and selectivity of the cycloaddition product, Like the [4+2] cycloaddition of other dienes and dienophiles, here also the HOMO and LUMO energy difference between the two polarophiles as well as the orbital-coefficient influence the selectivity of the addition product. Particularly in the case of heteroisobromzofuran, after the Diels-Alder reaction with dienophiles, the aromaticity-driven ring opening and elimination of water were also observed. In some cases, the reaction of heteroisombenzofuran with alkene, alkyne, and aryne was shown in Figure 3. The reactions of aryne and alkynes with heteroisobenzofuran provide the bridged addition product, which upon acid catalyzed rearrangement gave the phenolic compounds. On the other hand, reduction of the aforesaid bridged product with a reducing agent (e.g., $NaBH_4$) afforded the polynuclear hydrocarbon products.

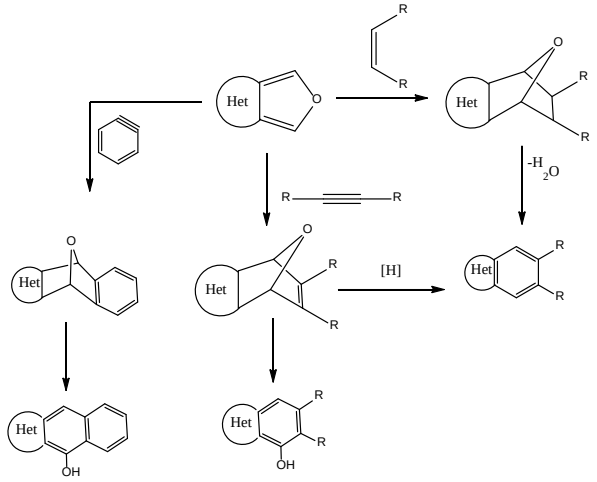

Figure 3: Reactivity Profile of Heteroisobenzofuran

Discussion

Natural product synthesis is a significant area of research, with benefits ranging from new scientific understanding to useful applications (Panda, 2019). Natural product synthesis is regarded by many as the pinnacle of organic synthesis and serves to establish the capabilities and limits of chemical synthesis at any specific period. It also contributes to the improvement of technology by striving to push the limits of molecular complexity, diversity, and efficiency. It is used to validate the structure, but it is also tested for novel synthetic techniques and occasionally used to help determine how the molecule is formed naturally. Although the application of isobenzofurans in the synthesis of natural products is quite high, in contrast to the use of hetero analogues, heteroisobenzofurans are comparatively less well documented in the literature. The application of heteroisobenzofurans as intermediates in the synthesis of natural and non-natural products is discussed below.

Synthesis of Ellipticine

The natural product ellipticine is a pyridocarbazole alkaloid that shows powerful anticancer properties. McKee and co-workers reported that Ellipticines have been shown to have fungicidal properties and have revealed promising results when tested against P. infestans growth (McKee *et al.,* 2020). The synthesis of ellipticine is one of the most intriguing uses of heteroisobenzofurans. Gribble and co-workers reported their first synthesis of ellipticine based on the cycloaddition reaction of 3,4-pyridyne and 1,3-dimethyl-4-(phenylsulfonyl)-4H-furo[3,4-b] indole (**2**) as the primary step (Figure 4) (Gribble *et al.,*1984). The [4+2] cycloaddition reaction provided the adduct as a 1:1 inseparable mixture of two regioisomers, 3 and 4, in a 38% overall yield. Reduction of the aforesaid mixture with $NaBH_4$ as a reducing agent in the presence of NaOH in a methanol solvent produced the desired natural product ellipticine 5 in a 23 % isolated yield along with the regioisomer isoellipticine 6 in a 29 % yield.

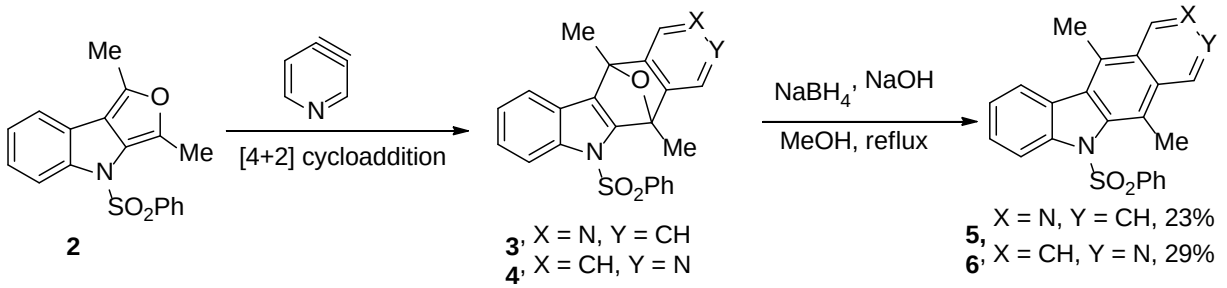

Figure 4: First Approach of Gribble's Synthesis of Ellipticine

In their second approach, Gribble *et al.* (1992) reported the trimethylsilyl trifluoromethanesulfonate-induced reaction between furoindole 2 and dihydropyridone 7 that produced lactam 8. The reaction is highly regioselective and produced lactam 8 in 89% yield (Figure 5). Reduction of lactam 8 with the strong reducing agent $LIAlH_4$ provides the cyclic amine, which is then dehydrogenated and debenzylated in the presence of a Pd/C catalyst to obtain the desired natural product ellipticine 5 in an 18% isolated yield.

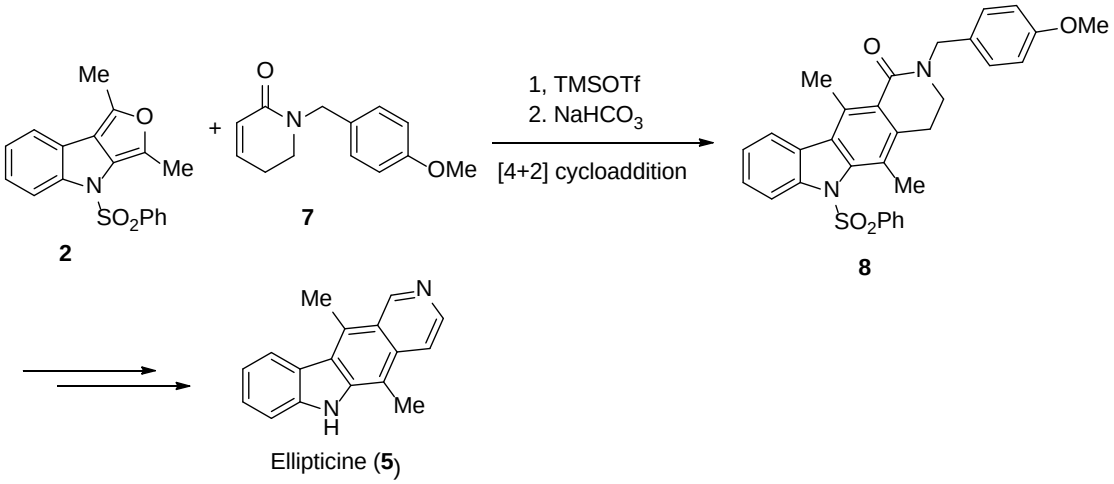

Figure 5: Second Approach of Gribble's Synthesis of Ellipticine

Diaz *et al.* (1998) described a polarity-controlled regioselective cycloaddition of 2-chloro 3, 4-pyridyne with heteroisobenzofuran and they used this reaction as a key step for the improved synthesis of ellipticine (Figure 6). This approach is a modified version of Gribble's method. The fluoride-promoted pyridine formation, followed by regiocontrol cycloaddition, provides the natural product ellipticine in a higher yield.

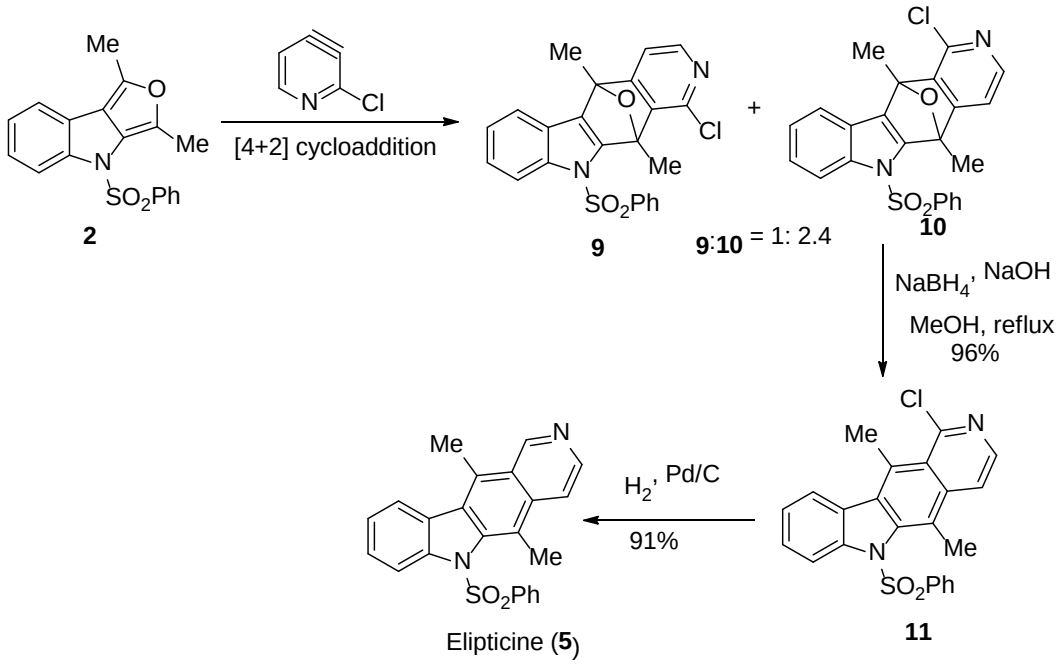

Figure 6: Guitian's Synthesis of Ellipticine

Synthesis of Murrayaquinone A

The natural product Murrayaquinone A is a carbazole alkaloid and it has been identified from the root bark of Murraya euchrestifolia Hayata. It shows cardiotonic activity on heart muscle.

Cagatay *et al.* (2021) was synthesize a series of Murrayaquinone A derivatives and found that these molecules have strong anti-cancer activity. Murrayaquinone A was synthesized by Miki and Hachiken in 1993 via a regioselective cycloaddition process between furo [3,4-blindole 14 and methyl acrylate 15 (Figure 7) (Miki & Hachiken, 1993). Their method entails the production of 4-benzyl-1-tert-butyldimethylsiloxy-4H-furo [3,4-blindole (14) by the deprotonation of lactone 13 by lithium bis (trimethylsilylamide, followed by o-silylation with tert-butyldimethylsilyl chloride (TBDMSCI), and regioselective trapping of this in-situ. After being treated with boron trifluoride etherate, the resulting adduct 16 produced methyl 9-
benzyl-4-hydroxycarbazole-3-carboxylate (17), which was then converted into murrayaquinone A 18.

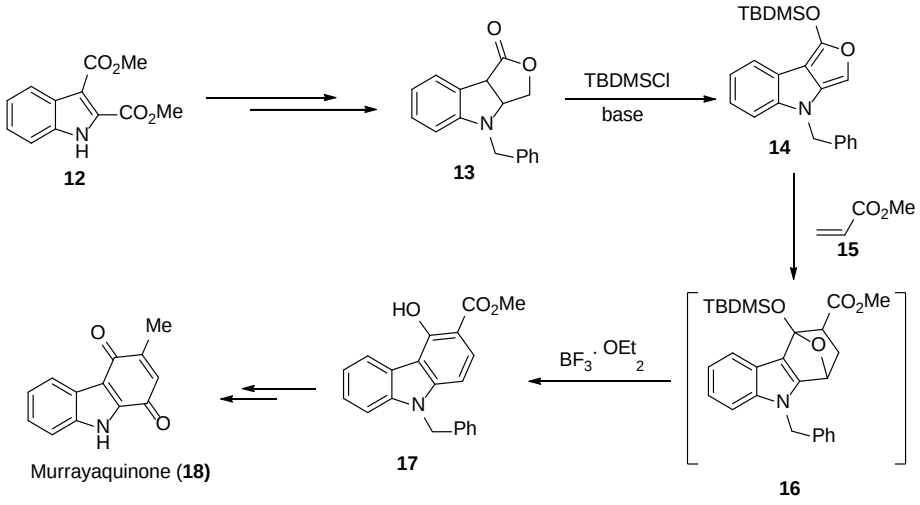

Figure 7: Synthesis of Murrayaquinone A

Synthesis of Heterolignans

In 1984, Masatomo and co-workers described a nice synthetic method for the synthesis of heterolignans, as shown in Figure 8 (Iwao, Inoue & Kuraishi, 1984). Sequential lithiation of pyridine-phthalide 19 with LDA followed by O-silylation with TBDMSCI results in the transitory intermediate 3-(silyloxy)pyrido [3,4-clfuran (20), which, when reacted with dimethyl fumarate, yields the stereoselective adducts 22 and 23 in lower yields. Para-toluenesulfonic acid-mediated reaction of the adduct 22 in benzene solvent under refluxing conditions provides the desired heterolignan 24 in good yield.

Moreover, Kuroda and co-workers have described the synthesis of heteroanalogues of 1-arylnaph-tulene lignans through the acid-catalyzed formation of a heteroisobenzofuran intermediate from an acetoxy-carbonyl molecule. Then this in-situ generated heteroisobenzofuran intermediate was reacted with dimethyl acetylenedicarboxylate through the [4+2] cycloaddition pathway to produce the heterolignan 28 (Figure 9) (Kuroda *et al.,* 1994). The thiolignan compound 28 exhibits potent antihyperlipidemic properties.

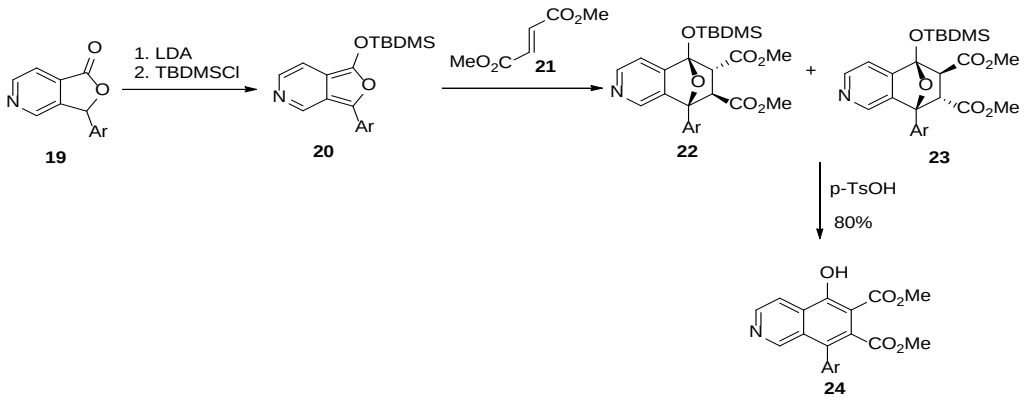

Figure 8: Synthesis of an Isoquinoline Lignan

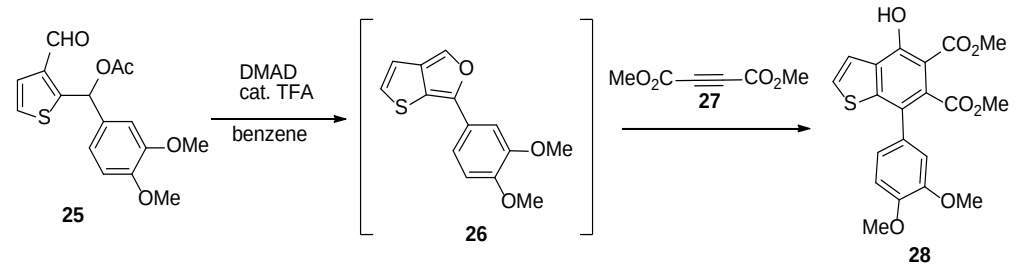

Figure 9: Synthesis of a Heterolignan

Synthesis of Conformationally Restricted Analogues of Nicotine and Anabasine

The chiral alkaloid nicotine is made up of two nitrogen-containing heterocycles, pyridine and N-methylpyrrolidine moieties, which are joined together by a single C-C bond. Since it is the most prevalent alkaloid that can be extracted from the dried leaves of the tobacco plants Nicotiana tabacum and Nicotiana rustica, nicotine is unquestionably one of the best-known naturally occurring N-heterocyclic compounds. Because of the possibility of pharmacological use in the treatment of Parkinson's disease, Alzheimer's disease, depression, and other disorders of the central nervous system, nicotine's clinical utility is restricted by its adverse effects on the heart, gastrointestinal tract, and neuromuscular systems, particularly its high potential for addiction.

There have been ongoing attempts at developing synthetic nicotine analogues that have been highly selective for particular nAChR subunits. Conformationally restricted derivatives, or changing the parent molecule in a way that severely restricts its original conformational mobility to one specific conformation, are of tremendous importance in this context (Panda & Albano, 2021). Because less entropy is lost when a ligand binds to a receptor, the ability to "freeze out" the conformational dynamics of a ligand might increase its affinity and specificity for that receptor. The pyridine and pyrrolidine moieties found in nicotine have been effectively linked with short chains comprised of simply carbon atoms or, in some circumstances, additionally including one or more heteroatoms to create a range of conformationally limited analogues of nicotine.

In the synthesis of conformationally constrained analogues of nicotine and anabasine, Sarkar and co-workers utilized the special benefit of intramolecular Diels-Alder chemistry of furo[3,4-c]-pyridines (Sarkar *et al.,* 2000). Due to their significance as neuronal acetylcholine receptors (nAChRs), nicotine and anabasine have gained interest in recent years. In their synthetic strategy, diazoacetic esters 29 and 30 are converted to the intermediate hetroisobenzofurans 31 and 32 through the $Rh_2(OAc)_4$-catalyzed reactions in benzene solvent under refluxing conditions for 1 hour. Finally, the ring opening reactions of compounds 33 and 34 perform successive proton transfer reactions to provide the biologically important molecules nicotine or anabasine in good yield (Figure 10).

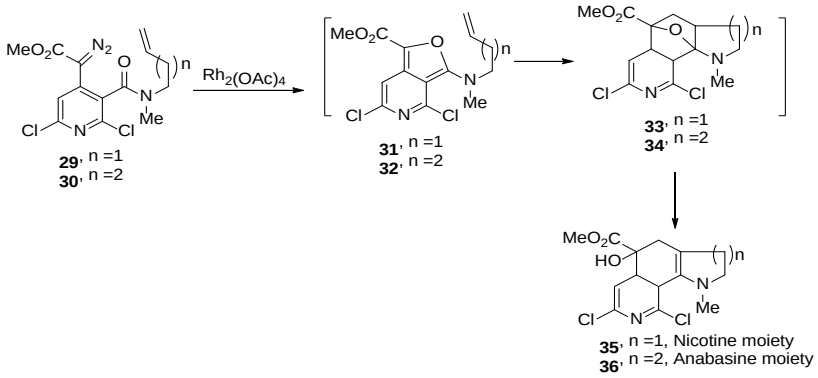

Figure 10: Synthesis of Conformationally Restricted Analogues of Nicotine and Anabasine

Synthesis of Aza-Homosteroid

In 2013, Roy and co-workers reported a novel method for the synthesis of aza-homosteroid moiety 40 via an intramolecular [4+2] cycloaddition reaction of aza-isobenzofuran 39 with a pendant alkene (Roy *et al.,* 2013) The intermediate aza-isobenzofuran 39 was generated by the reaction of γ, δ-unsaturated Fischer carbene complex with ortho-alkynyl heteroaryl carbonyl derivatives. The cycloaddition reaction in this case is highly regio- and stereoselective.

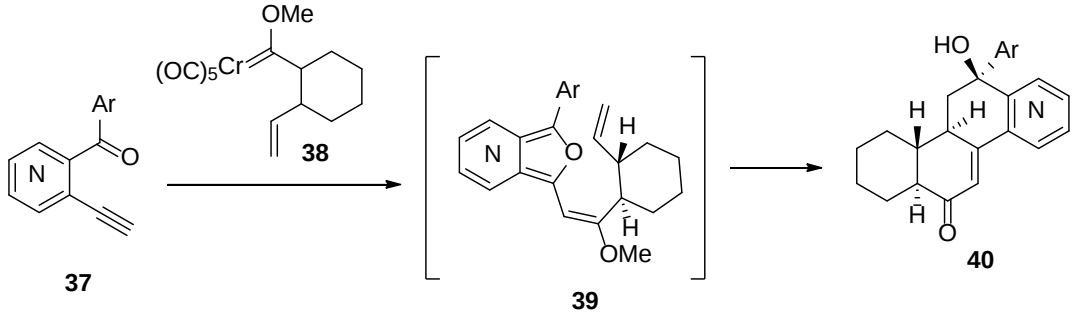

Figure 11: Synthesis of Aza-Homosteroid

Conclusion

In recent years, the chemistry of heteroisobenzofurans has seen a great surge of interest due to their potential for the synthesis of polycyclic heteroaromatics. In comparison to isobenzofurans, heteroaromatic isobenzofurans are still at an infant stage, and a lot of

possible compounds are yet to be developed. This challenge can be met by developing new heteroisobenzofurans and designing novel heteroaromatic assemblies with biological significance. Consequently, there has been an increase in research focused on this area. Natural products, such as those found in nature and those synthetically derived, have seen a huge rise in their importance, not only as pharmaceuticals but also as building blocks for complex molecules. As a result, the development of innovative synthetic strategies for generating heteroisobenzofuran natural products becomes highly desirable. In addition, efficient methods for the total synthesis of these compounds will have additional applications in drug discovery and medicinal chemistry. Thus, it is likely that this field of research will see advancements in both the number of novel compounds synthesized and the strategies employed for their synthesis in the upcoming years.

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